



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|   |           |  |
|---|-----------|--|
| <b>(51) International Patent Classification <sup>5</sup> :</b><br><b>A61K 31/74</b>   | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 94/27619</b><br><b>(43) International Publication Date:</b> 8 December 1994 (08.12.94)   |
| <b>(21) International Application Number:</b> PCT/US94/04538<br><b>(22) International Filing Date:</b> 25 April 1994 (25.04.94)<br><br><b>(30) Priority Data:</b><br>08/065,113      20 May 1993 (20.05.93)      US<br><br><b>(71) Applicant:</b> GELTEX, INC. [US/US]; 128 Spring Street, Lexington, MA 02173 (US).<br><br><b>(72) Inventors:</b> MANDEVILLE, W., Harry, III; 7 Pillings Road, Lynnfield, MA 01940 (US). HOLMES-FARLEY, Stephen, Randall; 20 Norfolk Road, Arlington, MA 02174 (US).<br><br><b>(74) Agent:</b> CLARK, Paul, T.; Fish & Richardson, 225 Franklin Street, Boston, MA 02110 (US). |           | <b>(81) Designated States:</b> AU, CA, JP, KR, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br><b>Published</b><br><i>With international search report.</i> |
| <b>(54) Title:</b> PROCESS FOR ADJUSTING ION CONCENTRATION IN A PATIENT AND COMPOSITIONS THEREFOR<br><br><b>(57) Abstract</b><br><br>A method of adjusting the concentration of selected ions in a patient by ion exchange that includes administering to the patient a therapeutically effective amount of one or more crosslinked polymers that are non-toxic and stable once ingested. The polymers are non-constipating and non-gritty such that irritation to the gastrointestinal tract upon ingestion is minimized.  |           |  |

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |  |    |                          |
|----|--------------------------|----|--|----|--------------------------|
| AT | Austria                  | GB | United Kingdom                           | MR | Mauritania               |
| AU | Australia                | GE | Georgia                                  | MW | Malawi                   |
| BB | Barbados                 | GN | Guinea                                   | NE | Niger                    |
| BE | Belgium                  | GR | Greece                                   | NL | Netherlands              |
| BF | Burkina Faso             | HU | Hungary                                  | NO | Norway                   |
| BG | Bulgaria                 | IE | Ireland                                  | NZ | New Zealand              |
| BJ | Benin                    | IT | Italy                                    | PL | Poland                   |
| BR | Brazil                   | JP | Japan                                    | PT | Portugal                 |
| BY | Belarus                  | KE | Kenya                                    | RO | Romania                  |
| CA | Canada                   | KG | Kyrgyzstan                               | RU | Russian Federation       |
| CF | Central African Republic | KP | Democratic People's Republic<br>of Korea | SD | Sudan                    |
| CG | Congo                    | KR | Republic of Korea                        | SE | Sweden                   |
| CH | Switzerland              | KZ | Kazakhstan                               | SI | Slovenia                 |
| CI | Côte d'Ivoire            | LI | Liechtenstein                            | SK | Slovakia                 |
| CM | Cameroon                 | LK | Sri Lanka                                | SN | Senegal                  |
| CN | China                    | LU | Luxembourg                               | TD | Chad                     |
| CS | Czechoslovakia           | LV | Latvia                                   | TG | Togo                     |
| CZ | Czech Republic           | MC | Monaco                                   | TJ | Tajikistan               |
| DE | Germany                  | MD | Republic of Moldova                      | TT | Trinidad and Tobago      |
| DK | Denmark                  | MG | Madagascar                               | UA | Ukraine                  |
| ES | Spain                    | ML | Mali                                     | US | United States of America |
| FI | Finland                  | MN | Mongolia                                 | UZ | Uzbekistan               |
| FR | France                   |    |  | VN | Viet Nam                 |
| GA | Gabon                    |    |  |    |                          |

- 1 -

PROCESS FOR ADJUSTING ION CONCENTRATION  
IN A PATIENT AND COMPOSITIONS THEREFOR

Background of the Invention

5        This invention relates to adjusting ion concentration in a patient.

      Disease states exist which are characterized by elevated concentrations of ions. Excess potassium ions, for example, are associated with renal failure, while  
10    excess sodium ions are associated with hypertension. Other disease states exist in which ion levels are depressed.

      Ion exchange resins which, when ingested, remove ions via the digestive tract are known. One such  
15    commercially available product is Kayexalate®, which is the sodium salt of a sulfonated polystyrene resin. When ingested, Kayexalate® exchanges its sodium ions in part for potassium ions and other cations present in the body. The resulting product (which is now the potassium salt of  
20    a sulfonated polystyrene resin) is then excreted from the body, thereby removing excess potassium ions.

Summary of the Invention

      In a first aspect, the invention features a method of adjusting the concentration of selected ions in a  
25    patient by ion exchange that includes administering to the patient a therapeutically effective amount of one or more crosslinked polymers that are non-toxic and stable once ingested. The polymers include units having one or more fixed (i.e., permanent) negatively charged sulfonate  
30    ( $-\text{SO}_3^-$ ), sulfate ( $-\text{OSO}_3^-$ ), phosphonate ( $-\text{PO}_3^{2-}$ ,  $-\text{PO}_3\text{H}^-$ ), phosphate ( $-\text{OPO}_3^{2-}$ ,  $-\text{OPO}_3\text{H}^-$ ), monocarboxylate ( $-\text{CO}_2^-$ ), or boronate ( $-\text{BO}_2\text{H}^-$ ,  $-\text{BO}_2^{2-}$ ) ions, and positively charged counterions other than hydrogen associated with these negatively charged ions that are exchangeable with ions  
35    in the gastrointestinal tract. The exchangeable

- 2 -

counterions may be the same as, or different from, each other. For example, the polymer may contain two different types of counterions, both of which are exchanged for ions in the gastrointestinal tract. More  
5 than one polymer, each having different counterions associated with the fixed charges, may be administered as well. The polymers are non-constipating and non-gritty (when measured relative to polymers such as Kayexalate® that are the sodium salts of sulfonated polystyrene  
10 resins) such that irritation to the gastrointestinal tract upon ingestion is minimized.

In a second aspect, the invention features a method of adjusting the concentration of selected ions in a patient by ion exchange that includes administering to  
15 the patient a therapeutically effective amount of one or more crosslinked polymers that are non-toxic and stable once ingested in which the polymers include units having one or more fixed (i.e., permanent) negatively charged polycarboxylate ions and positively charged counterions  
20 other than hydrogen or ammonium associated with these negatively charged ions that are exchangeable with ions in the gastrointestinal tract. The exchangeable counterions may be the same as, or different from, each other. For example, the polymer may contain two  
25 different types of counterions, both of which are exchanged for ions in the gastrointestinal tract. More than one polymer, each having different counterions associated with the fixed charges, may be administered as well. The polymers are non-constipating and non-gritty  
30 (when measured relative to polymers such as Kayexalate® that are the sodium salts of sulfonated polystyrene resins) such that irritation to the gastrointestinal tract upon ingestion is minimized.

By "non-toxic" it is meant that when ingested in  
35 therapeutically effective amounts neither the polymers

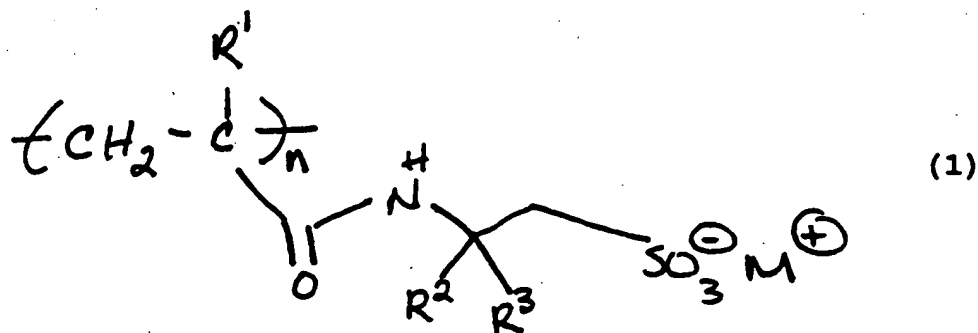
- 3 -

nor the ions released into the body upon ion exchange are harmful. Preferably, the ions released into the body are actually beneficial to the patient. Such is the case when, for example, the exchangeable cations are natural  
 5 nutrients such as amino acids, choline, and calcium.

By "stable" it is meant that when ingested in therapeutically effective amounts the polymers do not dissolve or otherwise decompose to form potentially harmful by-products, and remain substantially intact so  
 10 that they can transport ions following ion exchange out of the body.

In some preferred embodiments, the positively charged counterions include both non-metallic ions and metallic ions. Examples of suitable non-metallic ions  
 15 include ammonium, alkyl ammonium (e.g., containing between 1 and 4 C<sub>1</sub>-C<sub>5</sub> alkyl groups, trimethyl or triethyl ammonium), hydroxyalkylammonium (e.g., hydroxyethylammonium), hydroxyalkyl amino (e.g., hydroxyethyl amino), choline, taurine, carnitine,  
 20 guanidine, creatine, adenine, and amino acids (e.g., glycine, lysine, serine, arginine, alanine, histidine, or aspartic acid), or derivatives thereof (e.g., alkyl esters and amides) having a net positive charge. Examples of suitable metallic ions include sodium,  
 25 potassium, calcium, and magnesium.

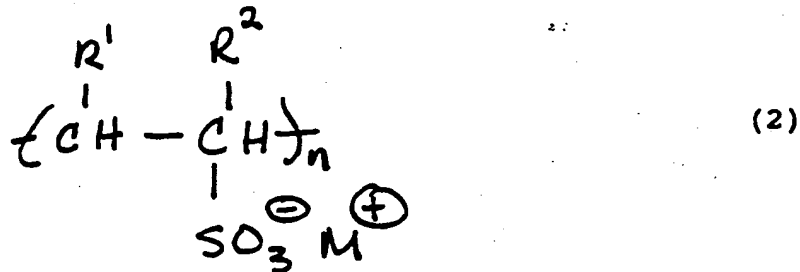
One example of a suitable polymer is characterized by a repeat unit having the formula



- 4 -

or a copolymer thereof (that includes these repeating units and one or more additional co-monomers), where  $n$  is an integer,  $M^+$  is an exchangeable counterion, and each  $R^1$ ,  $R^2$ , and  $R^3$ , independently, is H or a lower (e.g.,  $C_1$ - $C_5$ ) alkyl group (e.g., methyl). In a preferred polymer according to this formula,  $R^1$  is H,  $R^2$  is  $CH_3$ , and  $R^3$  is  $CH_3$ , and at least some the positively charged counterions include choline, sodium, hydroxyalkylammonium (e.g., ethanolammonium), or an amino acid (or derivative thereof).

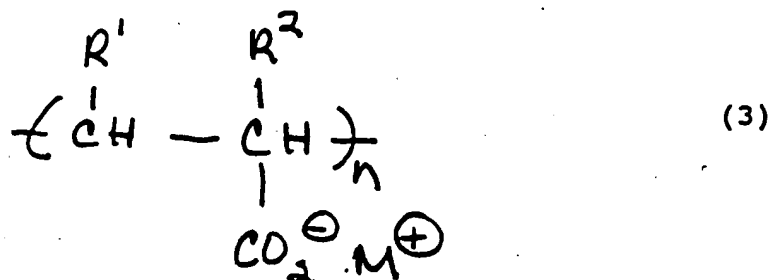
Another example is a polymer characterized by a repeat unit having the formula



or a copolymer thereof (that includes these repeating units and one or more additional co-monomers), where  $n$  is an integer,  $M^+$  is an exchangeable counterion, and each  $R^1$  and  $R^2$ , independently, is H or a lower (e.g.,  $C_1$ - $C_5$ ) alkyl group (e.g., methyl). In a preferred polymer according to this formula, at least some of the positively charged counterions include choline, sodium, hydroxylalkylammonium (e.g., ethanolammonium), or an amino acid (or derivative thereof).

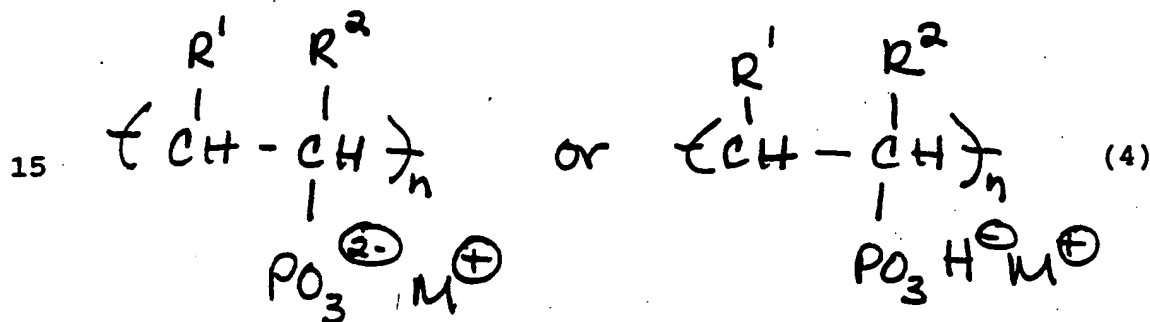
- 5 -

A third example is a polymer characterized by a repeat unit having the formula



or a copolymer thereof (that includes these repeating  
5 units and one or more additional co-monomers), where n is  
an integer, M<sup>+</sup> is an exchangeable counterion, and each R<sup>1</sup>  
and R<sup>2</sup>, independently, is H or a lower (e.g., C<sub>1</sub>-C<sub>5</sub>) alkyl  
group (e.g., methyl). In a preferred polymer according  
to this formula, at least some of the positively charged  
10 counterions include choline, sodium, hydroxyalkylammonium  
(e.g., ethanolammonium), or an amino acid (or derivative  
thereof).

A fourth example is a polymer characterized by a  
repeat unit having the formula

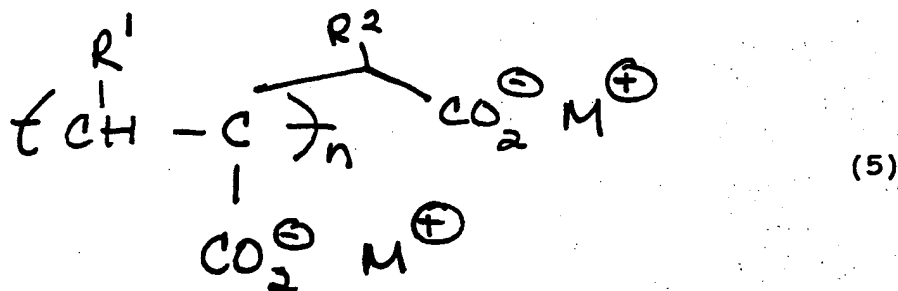


or a copolymer thereof (that includes these repeating  
units and one or more additional co-monomers), where n is  
an integer, M<sup>+</sup> is an exchangeable counterion, and each R<sup>1</sup>  
and R<sup>2</sup>, independently, is H or a lower (e.g., C<sub>1</sub>-C<sub>5</sub>) alkyl  
20 group (e.g., methyl). In a preferred polymer according  
to this formula, at least some the positively charged

- 6 -

counterions include choline, sodium, hydroxyalkylammonium (e.g., ethanolammonium), or an amino acid (or derivative thereof).

A fifth example is a polymer characterized by a repeat unit having the formula



or a copolymer thereof (that includes these repeating units and one or more additional co-monomers), where  $n$  is an integer,  $M^+$  is an exchangeable counterion, and each  $R^1$  and  $R^2$ , independently, is H or a lower (e.g.,  $C_1$ - $C_5$ ) alkyl group (e.g., methyl). In a preferred polymer according to this formula, at least some the positively charged counterions include choline, sodium, hydroxyalkylammonium (e.g., ethanolammonium), or an amino acid (or derivative thereof).

A fifth example is ethylene-maleic anhydride copolymer in which at least some of the positively charged counterions include choline, sodium, hydroxyalkylammonium (e.g., ethanolammonium), or an amino acid (or derivative thereof).

The invention also features therapeutic compositions that include a therapeutically effective amount of the above-described polymers. The polymers are particularly useful, e.g., for adjusting the concentration of potassium ions in a patient.

The invention provides an effective treatment for adjusting the concentration of one or more selected ions in a patient by ion exchange. The compositions are non-toxic and stable when ingested in therapeutically



- 7 -

effective amounts. They are also tasteless (in the absence of added flavoring) and odorless, as well as being non-constipating and non-gritty.

Other features and advantages will be apparent from the following description of the preferred embodiments thereof and from the claims.

#### Description of the Preferred Embodiments

##### Compositions

Preferred polymers have the formulae set forth in the Summary of the Invention, above. The polymers are crosslinked, making them insoluble and thereby limiting their activity to the gastrointestinal tract only. Thus, the polymers are non-systemic in their activity and will lead to reduced side-effects in the patient.

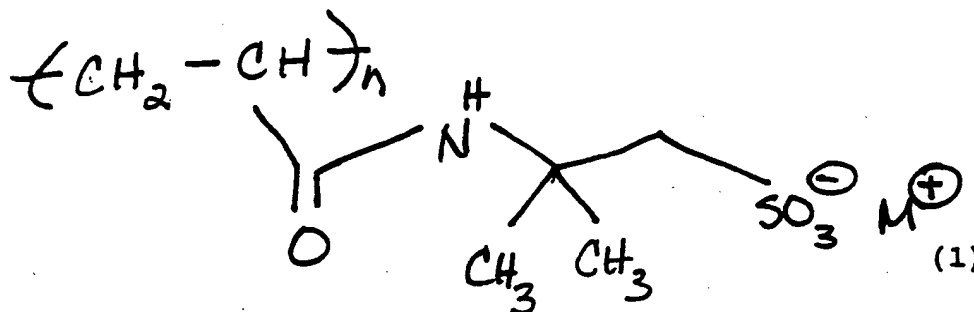
The polymers feature negatively charged fixed charges and positively charged exchangeable counterions (other than hydrogen) associated with these fixed charges. They are useful for altering the concentration of selected positively charged ions in the body, e.g., sodium, potassium, calcium, ammonium, copper, aluminum, and toxic heavy metal ions (e.g., cadmium, nickel, mercury, lead, and radioactive elements). Examples of suitable negatively charged fixed charges and positively charged counterions are set forth in the Summary of the Invention, above.

In addition to repeat units having negatively fixed charges and positively charged exchangeable counterions other than hydrogen, the polymers may contain additional co-monomers as well. The co-monomers may contain no fixed charges or they may feature other types of fixed charges and associated counterions (which may be, e.g., hydrogen ions). Examples of suitable co-monomers include, e.g., acrylamide and methacrylamide.

One example of a preferred polymer includes salts of poly-2-acrylamido-2-methylpropane sulfonic acid

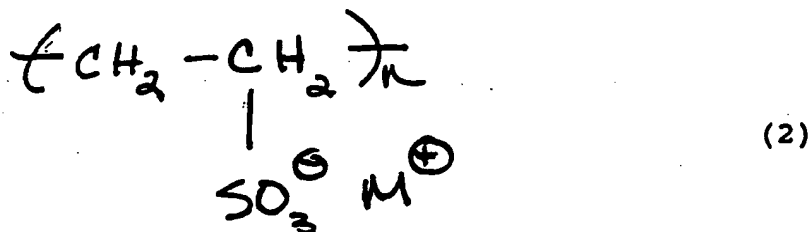
- 8 -

("AMPS"), which is a sulfonated derivative of polyacrylamide having the following formula (where  $M^+$  is an exchangeable counterion other than hydrogen):



5 or copolymers of AMPS and one or more additional co-  
monomers. The negatively charged fixed charges are the  
sulfonate groups (which are covalently attached to the  
polymer backbone). The polyacrylamide-based backbone  
contributes to the non-toxicity of these polymers when  
10 ingested in therapeutically effective amounts.

Another example of a preferred resin within this  
class includes salts of polyvinylsulfonic acid having the  
following formula (where  $M^+$  is an exchangeable counterion  
other than hydrogen):



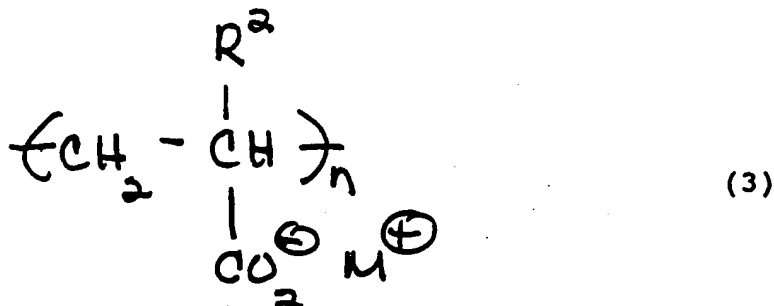
15

or copolymers of vinyl sulfonic acid and one or more  
additional co-monomers. The negatively charged fixed

- 9 -

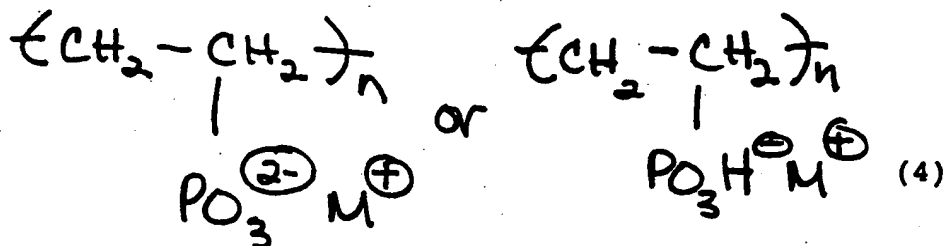
charges are sulfonate groups (which are covalently attached to the polymer backbone).

A third example of a preferred resin within this class includes salts of polyacrylic acid ( $R^2 = H$ ) and  
 5 polymethacrylic acid ( $R^2 = CH_3$ ) having the following formula (where  $M^+$  is an exchangeable counterion other than hydrogen):



or copolymers thereof formed with one or more additional  
 10 co-monomers, e.g., acrylamide or methacrylamide. The negatively charged fixed charges are monocarboxylate groups (which are covalently attached to the polymer backbone).

A fourth example of a preferred resin within this  
 15 class includes salts of polyvinylphosphonic acid, or copolymers of vinyl phosphonic acid having the following formula (where  $M^+$  is an exchangeable counterion other than hydrogen):



20 or copolymer of vinyl phosphonic acid and one or more additional co-monomers. The negatively charged fixed charges are phosphonate groups (which are covalently attached to the polymer backbone).

- 10 -

A fifth example of a preferred resin includes salts of polyitaconic acid, or copolymers of polyitaconic acid having the following formula (where  $M^+$  is an exchangeable counterion other than hydrogen or ammonium):



or copolymer of itaconic acid and one or more additional co-monomers. The negatively charged fixed charges are two carboxylate groups (which are covalently attached to the polymer backbone).

10 A sixth example of a preferred resin includes salts of ethylene-maleic anhydride copolymer (where  $M^+$  is an exchangeable counterion other than hydrogen or ammonium). The negatively charged fixed charges are two carboxylate groups (which are covalently attached to the  
15 polymer backbone).

The particular choice of counterion will depend in part on the ion concentration being adjusted. For example, in the case of potassium ion removal using PolyAMPS resins, choline has been found to be an  
20 effective exchangeable counterion.

The counterion may also be selected based upon its ability to supply needed ions (e.g., ions which are nutrients) to the body. For example, counterions such as amino acids, choline, and calcium are natural nutrients;  
25 thus, the invention provides a convenient way of supplying these beneficial materials to the patient while at the same time removing undesirable ions.

The ability to provide the polymer with two or more counterions that are different from each other, or

- 11 -

to administer mixtures of polymers, each having different counterions, makes it possible to devise a therapy designed to meet the needs of individual patients. Moreover, this ability makes it possible to replenish  
5 ions that may be removed from the body inadvertently during therapy. For example, in a polymer where the only counterion is choline both sodium and potassium ions will be exchanged for choline in the body and thus removed from the patient. This is a disadvantage if it is  
10 desired to remove only, e.g., sodium ions. However, by providing the polymer with both choline and, e.g., potassium ions, both of which exchange for sodium ions, any potassium ions exchanged for choline ions will be replenished by potassium ions from polymer exchanged for  
15 sodium ions.

The polymers are crosslinked, preferably by adding a crosslinking co-monomer to the reaction mixture during polymerization. Examples of suitable crosslinking co-monomers are diacrylates and dimethacrylates (e.g.,  
20 ethylene glycol diacrylate, propylene glycol diacrylate, butylene glycol diacrylate, ethylene glycol dimethacrylate, propylene glycol dimethacrylate, butylene glycol dimethacrylate, polyethyleneglycol dimethacrylate, polyethyleneglycol diacrylate), methylene bisacrylamide,  
25 methylene bismethacrylamide, ethylene bisacrylamide, ethylene bismethacrylamide, ethylidene bisacrylamide, N-allylacrylamide, divinyl benzene, bisphenol A dimethacrylate, and bisphenol A diacrylate. The amount of crosslinking co-monomer is typically between 2.5 and  
30 25 weight %, based upon combined weight of crosslinking co-monomer and other monomers, with 10% being preferred.

According to one method (particularly useful in the preparation of PolyAMPS resins), the resins are prepared by generating the monomer salt in situ, followed  
35 by polymerization in the presence of crosslinking co-

- 12 -

monomer and initiator, and purification to yield the product resin. According to another method, the monomer salt is combined with initiator and crosslinking comonomer, polymerized, and then purified.

## 5 Examples

### A. Preparation of Crosslinking Monomers

#### 1. Ethylenebisacrylamide (EDBA)

To a one liter, three-necked, round-bottomed flask was charged acryloyl chloride (18.10 g, 0.200 mol) and  
10 tetrahydrofuran (150 mL). The resulting solution was cooled to +5°C and a solution of ethylenediamine (12.20 g, 0.200 mol) in tetrahydrofuran (100 mL) was added dropwise to the acryloyl chloride solution over a period of two hours, keeping the temperature between +5° and  
15 +10°C. After the addition was completed, the mixture was stirred for an additional five minutes and then filtered. The filter cake was washed three times with 50 mL of tetrahydrofuran each time and the solid product, ethylenediamine monoacrylamide monohydrochloride was air  
20 dried to give 30.36 g (100%) of product. This material was used in the synthesis of the title compound without further purification as follows.

To a 500 mL three-necked, round-bottomed flask was charged ethylenediamine monoacrylamide monohydrochloride  
25 (15.06 g, 0.100 mol) and water (150 mL). Potassium hydroxide (6.40 g, 0.100 mol) was added until the pH of the solution was 7.5. The solution was cooled in an ice bath.

Another solution of potassium hydroxide (12.80 g, 0.100 mol) in water (40 mL) was prepared and acryloyl  
30 chloride (13.57 g, 0.15 mol) and the potassium hydroxide solution were added simultaneously, maintaining the pH at 7-8. When the addition was completed, the product was air dried overnight to give 7.97 g (47.4%) of crude

- 13 -

product. Purification was effected by recrystallization from water.

## 2. Ethylidenebisacrylamide (EBA)

To a one liter, three-necked, round-bottomed flask 5 was charged acrylamide (142.2 g, 2.00 mol), acetaldehyde (44.0 g, 1.00 mol, 60.0 mL), distilled water (400 mL), cupric acetate (0.30 g), and concentrated hydrochloric acid (35 mL). A slight exotherm (5°C) was observed upon addition of the hydrochloric acid. The reaction mixture 10 (which was clear) was then heated to 50°C and stirred overnight. When the temperature reached 46°C, product began to crystallize.

In the morning, the reaction mixture was cooled to room temperature and filtered. The filter cake was 15 washed three times with 100 mL of distilled water each time. The resulting product was then vacuum dried at 60°C to yield 89.9 g of ethylidenebisacrylamide (EBA).

## B. Polymer Preparation

- 20 1. Poly-2-acrylamido-2-methylpropane sulfonic acid, choline salt (Ch-AMPS) (choline hydroxide method)

To a 600 ml beaker was added acrylamidomethylpropane sulfonic acid (AMPS) (51.8 g, 0.250 mol), methylene bisacrylamide (5.8 g, 10 wt%), and 25 distilled water (200 mL) The mixture was stirred magnetically to effect dissolution. To this solution was added, with pH monitoring, 50% aqueous choline hydroxide (about 61 mL, 57 g, 0.250 mol) until a pH of 7.7 was achieved. The resulting solution was then covered with 30 Parafilm®, stirred magnetically, and degassed by bubbling nitrogen through it for 15 minutes. A thermometer inserted through the Parafilm® was used to measure the reaction temperature.

Next, a catalyst consisting of potassium 35 persulfate (0.7 g, 2.5 mmol) and sodium metabisulfite

- 14 -

(0.7 g, 3.5 mmol) was added to the solution all at once as solids. The polymerization proceeded almost immediately. The initial rate of temperature rise was 0.5°C/min and the maximum temperature achieved was 33°C.

5 The reaction gelled after 15 minutes.

The reaction mixture was allowed to stand overnight. In the morning, it was divided into four equal portions. One portion was placed in a blender and ethanol (650 mL) added to it. The resulting mixture was  
10 blended on high for a few seconds and then stirred on low for 5 minutes to dehydrate the gel. The resulting dehydrated gel was allowed to settle and the solvent decanted.

The blender procedure was repeated for each  
15 portion of the reaction mixture. All four portions were then combined in the blender and 1000 mL of ethanol added was added to make a total volume of 1300 mL. The resulting mixture was stirred for 10 minutes in the blender, after which the gel was allowed to settle.  
20 Next, the solvent was decanted and an additional 600 mL of ethanol added. The mixture was then stirred for 5 minutes and again allowed to settle, after which the last trituration was repeated. The product was then filtered, washed with ethanol, and vacuum dried to yield 73.3 g of  
25 crosslinked polymer.

2. Poly-2-acrylamido-2-methylpropane sulfonic acid, choline salt (Ch-AMPS) (choline chloride method)

To a 1000 ml flask was added  
30 acrylamidomethylpropane sulfonic acid (AMPS) (51.8 g, 0.250 mol), choline chloride (34.9 g, 0.250 mol) and ethanol (95%, denatured). The mixture was stirred to effect dissolution. To this solution was added dropwise, with pH monitoring, a solution of sodium hydroxide (11 g)  
35 and distilled water (30 mL). When the pH was 7.0, the addition was stopped and the mixture was stirred for an



- 15 -

addition 0.5 hour. Sodium chloride was then filtered off (4.1 g recovered, 28% of theoretical) and methylene bisacrylamide (MBA) (5.8 g, 10 wt% based upon combined weight of AMPS and MBA) was added to the ethanolic solution. The ethanol was then removed in vacuo using a rotary evaporator, after which the concentrate was quickly transferred to a 600 mL beaker using 250 mL of distilled water to aid the transfer; the water also acted as a solvent for the subsequent polymerization.

10       Next, a catalyst consisting of potassium persulfate (0.7 g, 2.5 mmol) and sodium metabisulfite (0.7 g, 3.5 mmol) was added to the solution with stirring as solids. The reaction mixture gelled in two minutes.

15       The reaction mixture was allowed to stand overnight. In the morning, it was divided into four equal portions. One portion was placed in a blender and ethanol (650 mL) added to it. The resulting mixture was blended on high for a few seconds and then stirred on low for 5 minutes to dehydrate the gel. The resulting  
20       dehydrated gel was allowed to settle and the solvent decanted.

25       The blender procedure was repeated for each portion of the reaction mixture. All four portions were then combined in the blender and 1000 mL of ethanol added was added to make a total volume of 1300 mL. The resulting mixture was stirred for 10 minutes in the blender, after which the gel was allowed to settle. Next, the solvent was decanted and an additional 600 mL of ethanol added. The mixture was then stirred for 5  
30       minutes and again allowed to settle, after which the last trituration was repeated. The product was then filtered, washed with ethanol, and vacuum dried to yield 72.0 g of crosslinked polymer.

- 16 -

3. Poly-2-acrylamido-2-methylpropane sulfonic acid, sodium salt (Na-AMPS)

To a 600 mL beaker was added acrylamidomethylpropane sulfonic acid (AMPS) (51.8 g, 5 0.250 mol) and distilled water (300 mL). Next, a solution containing sodium hydroxide (11 g) and distilled water (30 mL) was added dropwise to the AMPS solution with pH monitoring and stirring until a pH of 7.0 was attained. Methylene bisacrylamide (5.8 g, 10 wt%) was 10 then added to the solution, after which the resulting mixture was covered with Parafilm®, stirred magnetically, and degassed by bubbling nitrogen through it for 15 minutes. A thermometer inserted through the Parafilm® was used to measure the reaction temperature.

15 Next, a catalyst solution prepared by combining potassium persulfate (0.7 g, 2.5 mmol) in distilled water (30 mL) and sodium metabisulfite (0.7 g, 3.5 mmol) in distilled water (5 mL) was added to the solution all at once. The exothermic polymerization proceeded almost 20 immediately. The initial rate of temperature rise was 5.5°C/min and the maximum temperature achieved was 37°C. The reaction gelled after 5 minutes.

The reaction mixture was allowed to stand over the weekend. It was then transferred to a blender and 25 ethanol (800 mL) was added to it. The mixture was blended on high for a few seconds and then stirred on low for 5 minutes. The product was apparently swollen by ethanol since at this point it had not dehydrated.

Next, the ethanol slurry was removed from the 30 blender, divided into two equal portions (due to a limitation in blender volume), and an additional 400 mL of ethanol was added to each portion. Each portion was then blended separately to yield a sticky mass. The solvent was then decanted from the sticky mass and more 35 ethanol (400 mL) was added to each portion. Each

- 17 -

resulting portion was blended on high for a few seconds and then stirred on low for 5 minutes, after which each portion was filter, washed with ethanol, and vacuum dried to yield a combined total of 53.5 g of crosslinked polymer. The polymer had an equivalent weight of 254.7, corresponding to a functional density of 3.926 equiv/g.

4. Poly-2-acrylamido-2-methylpropane sulfonic acid, sodium salt (Na-AMPS)-Low Volume Method

To a 250 mL beaker was added acrylamidomethylpropane sulfonic acid (AMPS) (18.0 g), ethylidenebisacrylamide (2.0 g, 10 wt%), and distilled water (50 mL). Next, a solution containing sodium hydroxide (5 g) and distilled water (10 mL) was added dropwise to the AMPS solution with pH monitoring and stirring until a pH of 7.0 was attained. The temperature reached 65°C during neutralization.

The resulting mixture was covered with Parafilm®, stirred magnetically, and degassed by bubbling nitrogen through it for 15 minutes. A thermometer inserted through the Parafilm® was used to measure the reaction temperature.

Next, a catalyst consisting of potassium persulfate (0.1 g) and sodium metabisulfite (0.1 g) was added to the solution all at once as solids. The exothermic polymerization proceeded immediately. The reaction gelled after 20 seconds. The exotherm reached a maximum of 62°C (starting temperature 51.5°C) after three minutes.

The reaction mixture was allowed to stand overnight. It was then transferred to a blender and 2-propanol (150 mL) was added to it. The mixture was blended on high for a few seconds and then stirred on low for 5 minutes. The solvent was then decanted and another 200 mL of 2-propanol was added. The blending and decanting procedure was repeated two more times, with 200

- 18 -

mL of 2-propanol being added each time. The resulting slurry was then filtered, washed with 2-propanol, and vacuum dried to yield 26.2 g of polymer.

5           5.    Poly-2-acrylamido-2-methylpropane sulfonic acid, sodium salt (Na-AMPS)-Isopropanol Method

To a 250 mL beaker was added acrylamidomethylpropane sulfonic acid (AMPS) (27 g) and distilled water (54 mL). Next, a solution containing  
10 sodium hydroxide (6 g) and distilled water (10 mL) was added dropwise to the AMPS solution with pH monitoring and stirring until a pH of 7.0 was attained. The resulting solution was then added to a blender, after which 2-propanol (208 mL) and ethylidenebisacrylamide  
15 (3.0 g, 10 wt%) were added. The mixture was stirred slowly in the blender to dissolve the crosslinking agent. It was then degassed for 15 minutes with nitrogen.

Next, a catalyst solution prepared by combining potassium persulfate (0.1 g) and distilled water (5 mL)  
20 with sodium metabisulfite (0.1 g) and distilled water (3 mL) was added to the solution. After 15 seconds, the reaction mixture turned cloudy, indicating the polymerization was proceeding. The maximum reaction temperature of 29°C (starting temperature 25°C) was  
25 reached after four minutes.

After 30 minutes, 200 mL of 2-propanol was added and the mixture stirred for five minutes. The solid polymer was then filtered, washed with 2-propanol, and vacuum dried to afford 18.7 g of crosslinked polymer.

30           6.    Poly-2-acrylamido-2-methylpropane sulfonic acid, calcium salt (Ca-AMPS)

To a 250 mL beaker was added acrylamido-2-methylpropane sulfonic acid (AMPS) (20.7 g, 0.100 mol) and distilled water (160 mL). The solution was stirred

- 19 -

magnetically and calcium carbonate (5.0 g, 0.050 mol) was added with pH monitoring. The addition of calcium carbonate was stopped when a slight trace of the material did not dissolve. The final pH of the mixture was 4.93.

5 At this point, 2.50 g of the crosslinking agent methylenebisacrylamide (MBA) was added and the solution was warmed to 40°C to effect dissolution. During the warming period, the solution was degassed with nitrogen.

After 15 minutes of degassing, the catalyst,  
10 consisting of potassium persulfate (0.2 g) and sodium metabisulfite (0.2 g), was added. Following catalyst addition, the reaction exothermed from 45°C to 49°C, and then gelled over the course of 30 seconds. The resulting gel was allowed to harden overnight.

15 In the morning, the gel was transferred to a blender and 400 mL of isopropanol was added. The mixture was then blended on high for a few seconds, after which it was stirred on low for 5 minutes. Next, the solvent was decanted and the blending and decanting procedure was  
20 repeated two more times. The final mixture was then filtered, washed with isopropanol, and vacuum dried to afford 28.98 g of polymer.

7. Poly-2-acrylamido-2-methylpropane sulfonic acid, glycine salt (Gly-AMPS)

25 To a 250 mL beaker was added acrylamido-2-methylpropane sulfonic acid (AMPS) (20.7 g, 0.100 mol), glycine (7.51 g, 0.100 mol), methylenebisacrylamide (3.00 g), and distilled water (180 mL). The solution was warmed to 40°C to effect dissolution. During the warming  
30 period, the solution was degassed with nitrogen.

After 15 minutes of degassing, the catalyst, consisting of potassium persulfate (0.2 g) and sodium metabisulfite (0.2 g), was added. Following catalyst addition, the reaction exothermed from 37°C to 42°C, and

- 20 -

then gelled over the course of 75 seconds. The resulting gel was allowed to harden overnight.

In the morning, the gel was transferred to a blender and 400 mL of isopropanol was added. The mixture was then blended on high for a few seconds, after which it was stirred on low for 5 minutes. Next, the solvent was decanted and the blending and decanting procedure was repeated two more times. The final mixture was then filtered, washed with isopropanol, and vacuum dried to afford 36.11 g of polymer.

8. Poly-2-acrylamido-2-methylpropane sulfonic acid, lysine salt (Lys-AMPS)

To a 250 mL beaker was added acrylamido-2-methylpropane sulfonic acid (AMPS) (20.7 g, 0.100 mol), lysine (14.62 g, 0.100 mol), methylenebisacrylamide (2.30 g), and distilled water (180 mL). The solution was warmed to 37°C to effect dissolution. During the warming period, the solution was degassed with nitrogen.

After 15 minutes of degassing, the catalyst, consisting of potassium persulfate (0.2 g) and sodium metabisulfite (0.2 g), was added. Following catalyst addition, the reaction exothermed from 37°C to 41°C, and then gelled over the course of 60 seconds. The resulting gel was allowed to harden for four hours.

At the end of four hours, the gel was transferred to a blender and 400 mL of isopropanol was added. The mixture was then blended on high for a few seconds, after which it was stirred on low for 5 minutes. Next, the solvent was decanted and the blending and decanting procedure was repeated two more times. The final mixture was then filtered, washed with isopropanol, and vacuum dried to afford 39.24 g of polymer.

- 21 -

9. Poly-2-acrylamido-2-methylpropane sulfonic acid, serine salt (Ser-AMPS)

To a 250 mL beaker was added acrylamido-2-methylpropane sulfonic acid (AMPS) (20.7 g, 0.100 mol),  
5 serine (10.50 g, 0.100 mol), methylenebisacrylamide (2.30 g), and distilled water (180 mL). The solution was warmed to 34°C to effect dissolution. During the warming period, the solution was degassed with nitrogen.

After 15 minutes of degassing, the catalyst,  
10 consisting of potassium persulfate (0.2 g) and sodium metabisulfite (0.2 g), was added. Following catalyst addition, the reaction exothermed from 34°C to 39°C, and then gelled over the course of 3 minutes. The resulting gel was allowed to harden overnight.

15 In the morning, the gel was transferred to a blender and 800 mL of isopropanol was added. The mixture was then blended on high for a few seconds, after which it was stirred on low for 5 minutes. Next, the solvent was decanted and the blending and decanting procedure was  
20 repeated two more times using 400 mL of isopropanol each time. The final mixture was then filtered, washed with isopropanol, and vacuum dried to afford 38.23 g of polymer.

25 10. Poly-2-acrylamido-2-methylpropane sulfonic acid, alanine salt (Ala-AMPS)

To a 250 mL beaker was added acrylamido-2-methylpropane sulfonic acid (AMPS) (20.7 g, 0.100 mol),  
alanine (8.91 g, 0.100 mol), methylenebisacrylamide (2.30 g), and distilled water (180 mL). The solution was  
30 warmed to 34°C to effect dissolution. During the warming period, the solution was degassed with nitrogen.

After 15 minutes of degassing, the catalyst,  
consisting of potassium persulfate (0.2 g) and sodium metabisulfite (0.2 g), was added. Following catalyst  
35 addition, the reaction exothermed from 34°C to 38°C, and

- 22 -

then gelled over the course of 2.5 minutes. The resulting gel was allowed to harden overnight.

In the morning, the gel was transferred to a blender and 1000 mL of isopropanol was added. The mixture was then blended on high for a few seconds, after which it was stirred on low for 5 minutes. Next, the solvent was decanted and the blending and decanting procedure was repeated two more times using 400 mL of isopropanol each time. The final mixture was then filtered, washed with isopropanol, and vacuum dried to afford 29.36 g of polymer.

11. Poly(Sodium Vinyl Sulfonate) (Solvent Method)

Dry solid sodium vinyl sulfonate (SVS; 5.0 g) was suspended in 20 mL of denatured ethanol (90% ethanol, 5% methanol, 5% isopropanol) in a one-necked, round bottomed flask equipped with a reflux condenser.

Methylenebismethacrylamide (0.5 g) and AIBN (0.1 g) were added and the mixture was heated to reflux under nitrogen. The mixture was refluxed for six hours under nitrogen and then allowed to cool to room temperature. Denatured ethanol (100 mL) was added and the solution stirred for 5 minutes. The solid suspended in the ethanol was collected by filtration. The collected solid was suspended in 500 mL of water and stirred for 20 minutes and then centrifuged. The solid residue was collected and vacuum dried to afford 1.53 g of polymer.

12. Poly(Sodium Vinyl Sulfonate) (Aqueous Method)

Aqueous sodium vinyl sulfonate (11.63 g of SVS as a 40.8% by weight aqueous solution) was combined with N-allylacrylamide (0.5 g) and sealed under vacuum in a 200 mL vacuum flask. The flask was cooled to 5°C and exposed to ultraviolet light (354 nm; ~180 mW/cm<sup>2</sup>) for 72 h. The resulting gel was removed from the flask and blended with



- 23 -

500 mL of isopropanol. After settling, the liquid was poured off and 500 mL of isopropanol was again added. After blending, settling, and pouring off the isopropanol twice more, the solid was collected by filtration. The solid was partially dried in vacuum to afford 15.0 g of crude polymer.

The polymer was suspended in water (100 mL) and after stirring for 5 minutes, methanol (100 mL) was added. The solution was allowed to settle and the clear liquid was poured off to leave a white solid. The solid was dispersed in 500 mL of water and stirred for 40 minutes. Methanol (500 mL) was added and the solids were collected by centrifugation. The solids were vacuum dried to afford 4.68 g of polymer.

In a variation of this method, methylenebisacrylamide (0.5 g) was used as a crosslinking co-monomer instead of N-allylacrylamide. Exposure to UV light was at room temperature for 18 h. This method afforded 5.42 g of polymer.

13. Poly(Choline Vinyl Sulfonate) (Direct Polymerization Method)

Sodium vinyl sulfonate (200 mL of 25% w/w aqueous solution) was combined with choline chloride (63.1 g) in a 2 L flask and stirred for 5 minutes. Methanol (400 mL) and then isopropanol (800 mL) were added with stirring. The resulting white precipitate was filtered off and discarded. The remaining clear liquid was reduced on a rotary evaporator to a total weight of 125.2 g, at which point solid was beginning to precipitate. The solid was filtered off and 114.5 g of a clear viscous liquid remained.

The liquid was combined with methylenebisacrylamide (5.3 g) in a 1 L reaction kettle and warmed slightly to encourage dissolution (complete dissolution was not

- 24 -

attained). The kettle was evacuated and exposed to UV light (365 nm; ~7000 mW/cm<sup>2</sup>) for 72 h.

After exposure the gel was removed, blended with 700 mL of isopropanol, and the liquid poured off. The fine  
5 white solids were suspended in 1 L of water, stirred for 1 h, and collected by centrifugation. The solids were again suspended in 1 L of water, stirred for 1 h, and collected. The solids were vacuum dried to afford 18.2 g of polymer.

10        14. Poly(Choline Vinyl Sulfonate) (Ion Exchange Method)

Dry solid poly(sodium vinyl sulfonate) (4.0 g made by the Ion Exchange Method) was ground in an electric coffee grinder and sieved to afford 3.61 g of -80/+200  
15 mesh particles. These particles were suspended in 400 mL of 1 M aqueous choline chloride and stirred for 2 h. The solid was collected by centrifugation and the suspension/centrifugation process repeated twice more. The solid was vacuum dried to afford 6.82 g of crude  
20 polymer.

The crude polymer was suspended in 500 mL of water, stirred for 2 h, and the solid collected by filtration. This process was repeated with a second batch of 500 mL of water, and the collected solids were vacuum dried to  
25 afford 4.05 g of polymer. Analysis of the product indicated that it contained less than 0.1% sodium by weight.

15. Poly(Choline Vinyl Phosphonate)

Vinylphosphonic acid (52.3 g of 90% w/w solution)  
30 was combined with methylenebisacrylamide (5.2 g) in a 1 L reaction kettle. The kettle was evacuated and the mixture was heated to speed dissolution. The kettle was exposed to UV light (365 nm; ~7000 mW/cm<sup>2</sup>) at room temperature for 72 h. Air had leaked into the kettle

- 25 -

such that by the end of the experiment it was no longer under vacuum. The resulting gel was removed and blended with 600 mL of isopropanol. After pouring off the liquid, the solids were again blended with 600 mL of isopropanol. The solids were collected by filtration and partially dried in vacuum.

The resulting solids were ground in an electric coffee grinder and suspended in 400 mL of water. The pH of this solution was 1.27. Choline bicarbonate (75% w/w aqueous) was added until the pH reached 6.5 (approximately 44 g of 75% solution was added). The solids were collected by filtration with the addition of denatured ethanol (~2 L) to aid filtration by collapsing the gel. The solid was rinsed twice with 500 mL of denatured ethanol and vacuum dried to afford 23.81 g of polymer.

#### 16. Crosslinked Polyacrylamide (control)

To a 600 ml beaker was added acrylamide (35.5 g, 0.500 mol), methylene bisacrylamide (3.9 g, 9.9 wt%), and distilled water (170 mL). The mixture was covered with Parafilm®, stirred magnetically, and degassed by bubbling nitrogen through it for 15 minutes. A thermometer inserted through the Parafilm® was used to measure the reaction temperature.

Next, a catalyst solution prepared by combining potassium persulfate (1.3 g, 5 mmol) and distilled water (50 mL) with sodium metabisulfite (1.3 g, 7 mmol) and distilled water (8 mL) was added to the solution all at once. The strongly exothermic polymerization proceeded almost immediately. The reaction gelled after 1 minute.

The reaction mixture was allowed to stand overnight. In the morning, it was transferred to a blender and methanol (350 mL) was added. The resulting mixture was blended on high for a few seconds. It was then decanted

- 26 -

and an additional 400 mL of methanol was added. The resulting mixture was then blended on high for a few seconds and then on low for 5 minutes. The resulting granular, dehydrated polymer was filtered, washed with 5 methanol, and air-dried to yield 44.6 g of crosslinked polymer.

In order to ensure that no residual monomer was left in the product, it was then triturated 3 times with methanol for a minimum of 2 hours each time. The product 10 was then air-dried to yield 40.8 g of crosslinked polymer.

#### Use

The polymers according to the invention may be administered orally to a patient in a dosage of about 1 15 mg/kg/day to about 10 g/kg/day; the particular dosage will depend on the individual patient (e.g., the patient's weight and the extent of ion addition or removal required). The polymer may be administered either in hydrated or dehydrated form, and may be 20 flavored if necessary to enhance patient acceptability; additional ingredients such as artificial coloring agents may be added as well.

Examples of suitable forms for administration include pills, tablets, capsules, and powders (for 25 sprinkling on food). The pill, tablet, capsule, or powder can be coated with a substance capable of protecting the composition from the gastric acid in the patient's stomach for a period of time sufficient to allow the composition to pass undisintegrated into the 30 patient's small intestine. The polymer may be administered alone or in combination with a pharmaceutically acceptable carrier substance, e.g., magnesium carbonate, lactose, or a phospholipid with which the polymer can form a micelle.

- 27 -

The in vitro potassium ion removal capabilities of various polymers were evaluated and (in some cases) compared to Kayexalate® and crosslinked polyacrylamide (prepared as described above) as follows.

- 5 To a 40 mL centrifuge tube was added 0.50 g of polymer resin and 40 mL of artificial colonic fluid. This fluid, which is designed to simulate the physiological environment found in the digestive tract, consisted of the following:

| 10 | <u>Cations (concentration)</u> | <u>Anions</u>  |
|----|--------------------------------|--|
|    | <u>(concentration)</u>         |  |
|    | Na <sup>+</sup> (40 mmol)      | Cl <sup>-</sup> (19 mmol)                              |
|    | K <sup>+</sup> (90 mmol)       | HCO <sub>3</sub> <sup>-</sup> (30 mmol)                |
|    | Mg <sup>++</sup> (2 mmol)      | H <sub>2</sub> PO <sub>4</sub> <sup>-</sup> (3 mmol)   |
| 15 | Ca <sup>++</sup> (2 mmol)      | CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup> (82 mmol) |

- The mixture was shaken vigorously to disperse the polymer and then stirred at room temperature for two hours, after which it was centrifuged and decanted. The supernatant liquid was decanted and discarded. The wet, swollen polymer was then scraped out of the tube, weighed, vacuum dried, and weighed again. The dry polymer was sent to Schwartzkopf Laboratories for sodium and potassium analysis. The results are shown in Table 1 under the heading "centrifuged, unwashed samples." All values are normalized per gram of polymer. The percentage crosslinked refers to the weight percentage of crosslinking co-monomer (MBA or EBA) added.

Evaluation of Polymers for Ion Exchange of Potassium to Effect Removal From the Body

| 30                                   | 10% cross-linked  |                |                |
|--------------------------------------|-------------------|----------------|----------------|
|                                      | <u>Kayexalate</u> | <u>Ch-AMPS</u> | <u>Na-AMPS</u> |
| <u>Centrifuged, unwashed samples</u> |                   |                |                |
| meg Na/g resin                       | 2.29              | 1.10           | 2.65           |
| meg K/g resin                        | 2.06              | 2.96           | 2.24           |

- 28 -

10% cross-linked

|                                      | <u>Na-AMPS</u><br><u>Low Vol</u> | <u>Na-AMPS</u><br><u>i-PrOH</u> | Acrylamide |
|--------------------------------------|----------------------------------|---------------------------------|------------|
| <u>Centrifuged, unwashed samples</u> |                                  |                                 |            |
| 5 meg Na/g resin                     | 2.18                             | 2.43                            | 0.66       |
| meg K/g resin                        | 2.36                             | 2.40                            | 1.14       |

Evaluation of Polymers for Ion Exchange of Potassium to Effect Removal From the Body  
(Four Exchanges)

|                                      |                |                                    |                                  |
|--------------------------------------|----------------|------------------------------------|----------------------------------|
| 10                                   |                | Four exchanges<br>10% cross-linked |                                  |
|                                      | Kayexalate     | <u>Ch-AMPS</u><br><u>IPN</u>       | <u>Na-AMPS</u><br><u>Low Vol</u> |
| <u>Centrifuged, unwashed samples</u> |                |                                    |                                  |
|                                      | meg Na/g resin | 0.89                               | 1.45                             |
| 15                                   | meg K/g resin  | 2.38                               | 3.20                             |

Evaluation of Polymers for Ion Exchange of Potassium to Effect Removal From the Body

|    |                                      |                         |                           |
|----|--------------------------------------|-------------------------|---------------------------|
|    |                                      | 10% cross-linked        |                           |
|    | <u>Na-VSA<sup>1</sup></u>            | <u>K-AA<sup>2</sup></u> | <u>Ch-VPA<sup>3</sup></u> |
| 20 | <u>Centrifuged, unwashed samples</u> |                         |                           |
|    | meg Na/g resin                       | 2.19                    | 2.26                      |
|    | meg K/g resin                        | 4.99                    | 4.82                      |

<sup>1</sup> polyvinyl sulfonic acid, sodium salt

<sup>2</sup> polyacrylic acid, potassium salt

25 <sup>3</sup> polyvinyl phosphonic acid, choline salt

Other embodiments are within the following claims.

What is claimed is:

- 29 -

CLAIMS

1. A method of adjusting the concentration of selected ions in a patient by ion exchange comprising administering to said patient a therapeutically effective  
5 amount of one or more crosslinked polymers that are non-toxic and stable once ingested,

said polymers comprising units having fixed negatively charged sulfonate, sulfate, phosphonate, phosphate, monocarboxylate, or boronate ions, and  
10 positively charged counterions other than hydrogen which may be the same or different from each other associated with said negatively charged ions that are exchangeable with ions in the gastrointestinal tract,

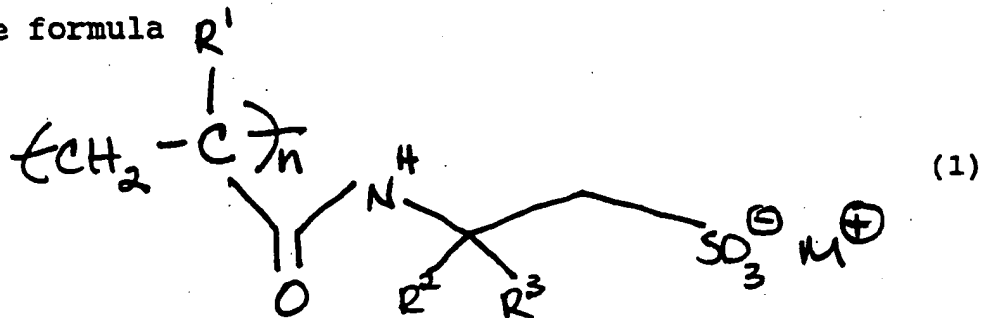
said polymers having the property of being non-  
15 constipating and non-gritty such that irritation to the gastrointestinal tract upon ingestion is minimized.

2. The method of claim 1 wherein at least some of said positively charged counterions are non-metallic ions comprising ammonium, alkyl ammonium, hydroxyalkyl  
20 ammonium, choline, taurine, carnitine, guanidine, creatine, adenine, or amino acids or derivatives thereof having a net positive charge.

3. The method of claim 2 wherein said amino acid comprises glycine, lysine, serine, arginine, alanine,  
25 histidine, or aspartic acid.

4. The method of claim 1 wherein at least some of said positively charged counterions are metallic ions comprising sodium, potassium, calcium, or magnesium.

5. The method of claim 1 wherein at least one of said polymers is characterized by a repeat unit having the formula  $P'$

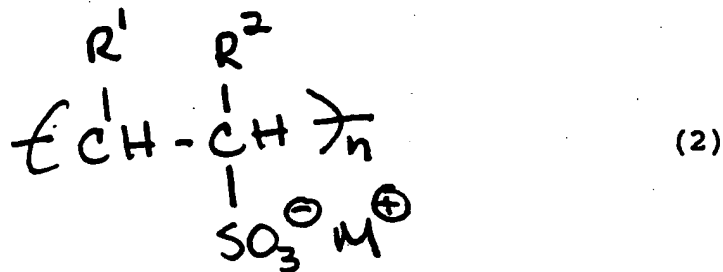


5 or copolymer thereof, where n is an integer,  $M^+$  is an exchangeable counterion other than hydrogen, and each  $R^1$ ,  $R^2$ , and  $R^3$ , independently, is H or a lower alkyl group.

6. The method of claim 5 wherein  $R^1$  is H,  $R^2$  is  $CH_3$ , and  $R^3$  is  $CH_3$ .

10           7. The method of claim 5 wherein at least some of said positively charged counterions comprise choline, sodium, hydroxyalkylammonium, or an amino acid or derivative thereof.

8. The method of claim 1 wherein at least one of  
15 said polymers is characterized by a repeat unit having  
the formula



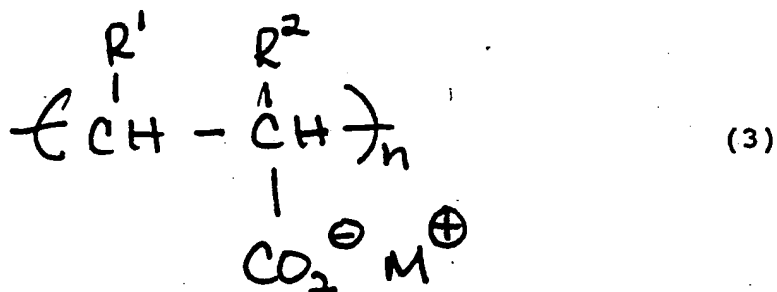
or copolymer thereof, where n is an integer, M<sup>+</sup> is an exchangeable counterion other than hydrogen, and each R<sup>1</sup> and R<sup>2</sup>, independently, is H or a lower alkyl group.



- 31 -

9. The method of claim 8 wherein at least some of said positively charged counterions comprise choline, sodium, hydroxyalkylammonium, or an amino acid or derivative thereof.

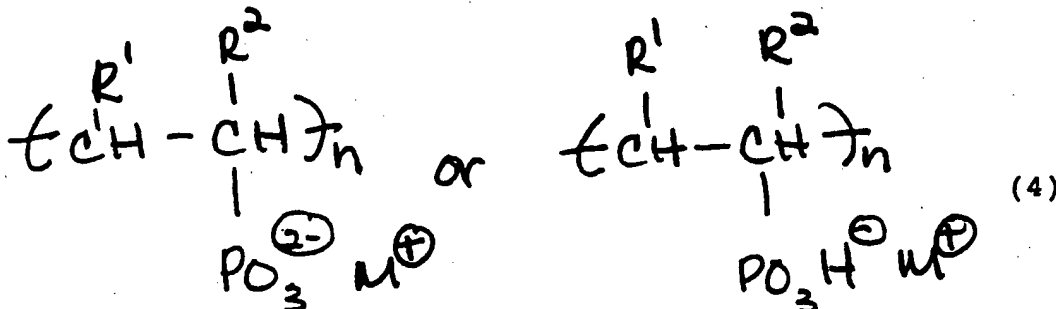
5 10. The method of claim 1 wherein at least one of said polymers is characterized by a repeat unit having the formula



where n is an integer,  $M^+$  is an exchangeable counterion  
 10 other than hydrogen, and each  $R^1$  and  $R^2$ , independently, is H or a lower alkyl group.

11. The method of claim 10 wherein at least some of said positively charged counterions comprise choline,  
 sodium, hydroxylalkylammonium, or an amino acid or  
 15 derivative thereof.

12. The method of claim 1 wherein at least one of said polymers is characterized by a repeat unit having the formula



- 32 -

where  $n$  is an integer,  $M^+$  is an exchangeable counterion other than hydrogen, and each  $R^1$  and  $R^2$ , independently, is H or a lower alkyl group.

13. The method of claim 12 wherein at least some of  
5 said positively charged counterions comprise choline, sodium, hydroxyalkylammonium, or an amino acid or derivative thereof.

14. The method of claim 1 wherein there are at  
least two different positively charged counterions  
10 associated with said fixed negatively charged ions.

15. A method of adjusting the concentration of potassium ions in a patient by ion exchange comprising administering to said patient a therapeutically effective amount of one or more crosslinked polymers that are non-  
15 toxic and stable once ingested,

said polymers comprising units having fixed negatively charged sulfonate, sulfate, phosphonate, phosphate, monocarboxylate, or boronate ions, and positively charged counterions other than hydrogen which  
20 may be the same or different from each other associated with said negatively charged ions that are exchangeable with potassium ions in the gastrointestinal tract,

said polymers having the property of being non-constipating and non-gritty such that irritation to the  
25 gastrointestinal tract upon ingestion is minimized.

16. A therapeutic composition comprising a therapeutically effective amount of one or more crosslinked polymers that are non-toxic and stable once ingested,

- 33 -

said polymers comprising units having fixed negatively charged sulfonate, sulfate, phosphonate, phosphate, monocarboxylate, or boronate ions, and positively charged counterions other than hydrogen which  
 5 may be the same or different from each other associated with said negatively charged ions that are exchangeable with ions in the gastrointestinal tract,

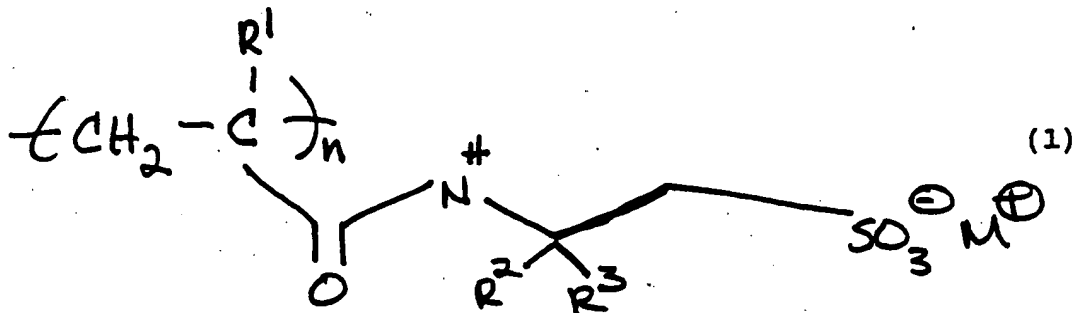
said composition having the property of being non-constipating and non-gritty such that irritation to the  
 10 gastrointestinal tract upon ingestion is minimized.

17. The composition of claim 16 wherein at least some of said positively charged counterions are non-metallic ions comprising ammonium, alkyl ammonium, hydroxyalkyl ammonium, choline, taurine, carnitine,  
 15 guanidine, creatine, adenine, or amino acids or derivatives thereof having a net positive charge.

18. The composition of claim 17 wherein said amino acid comprises glycine, lysine, serine, arginine, alanine, histidine, or aspartic acid.  
 20

19. The composition of claim 16 wherein at least some of said positively charged counterions are metallic ions comprising sodium, potassium, calcium, or magnesium.

20. The composition of claim 16 wherein at least  
 25 one of said polymers is characterized by a repeat unit having the formula



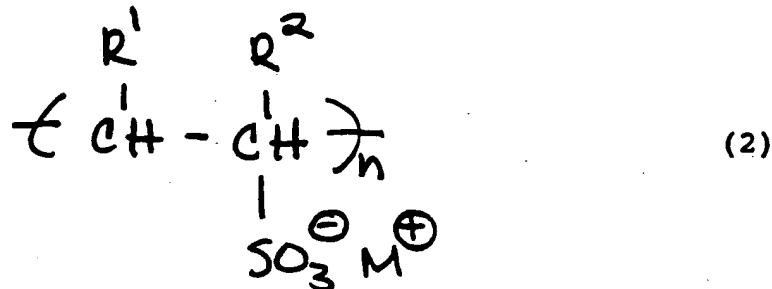
- 34 -

or copolymer thereof, where n is an integer,  $M^+$  is an exchangeable counterion other than hydrogen, and each  $R^1$ ,  $R^2$ , and  $R^3$ , independently, is H or a lower alkyl group.

21. The composition of claim 20 wherein  $R^1$  is H,  $R^2$  is  $CH_3$ , and  $R^3$  is  $CH_3$ .

22. The composition of claim 20 wherein at least some of said positively charged counterions comprise choline, sodium, hydroxyalkylammonium, or an amino acid or derivative thereof.

23. The composition of claim 1 wherein at least one of said polymers is characterized by a repeat unit having the formula

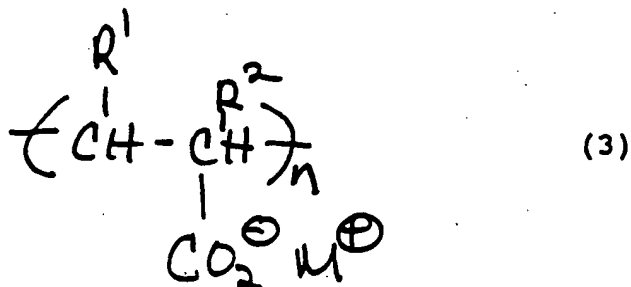


or copolymer thereof, where n is an integer,  $M^+$  is an exchangeable counterion other than hydrogen, and each  $R^1$  and  $R^2$ , independently, is H or a lower alkyl group.

24. The composition of claim 23 wherein at least some of said positively charged counterions comprise choline, sodium, hydroxyalkylammonium or an amino acid, or a derivative thereof.

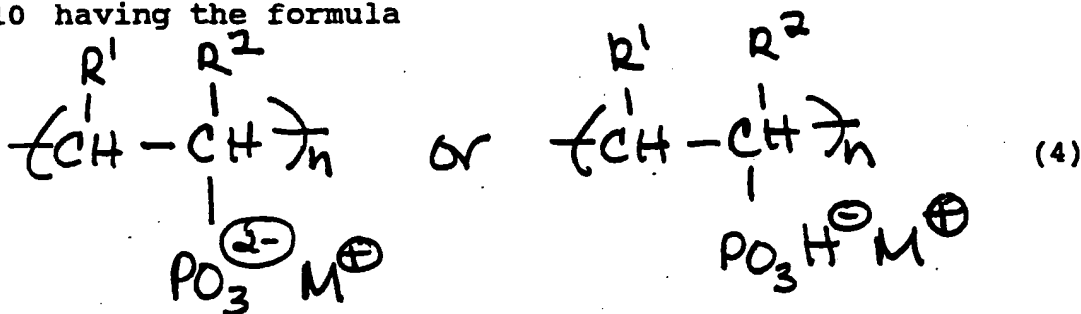
- 35 -

25. The composition of claim 16 wherein at least one of said polymers is characterized by a repeat unit having the formula



5 where n is an integer,  $M^+$  is an exchangeable counterion other than hydrogen, and each  $R^1$  and  $R^2$ , independently, is H or a lower alkyl group.

26. The composition of claim 16 wherein at least one of said polymers is characterized by a repeat unit  
10 having the formula



where n is an integer,  $M^+$  is an exchangeable counterion other than hydrogen, and each  $R^1$  and  $R^2$ , independently, is H or a lower alkyl group.

15 27. The composition of claim 26 wherein at least some of said positively charged counterions comprise choline, sodium, hydroxyalkylammonium or an amino acid, or a derivative thereof.

28. The composition of claim 16 wherein there are  
20 at least two different positively charged counterions associated with said fixed negatively charged ions.

- 36 -

29. A method of adjusting the concentration of selected ions in a patient by ion exchange comprising administering to said patient a therapeutically effective amount of one or more crosslinked polymers that are non-  
5 toxic and stable once ingested,

said polymers comprising units having fixed negatively charged polycarboxylate ions, and positively charged counterions other than hydrogen or ammonium which may be the same or different from each other associated  
10 with said negatively charged ions that are exchangeable with ions in the gastrointestinal tract,

said polymers having the property of being non-constipating and non-gritty such that irritation to the gastrointestinal tract upon ingestion is minimized.

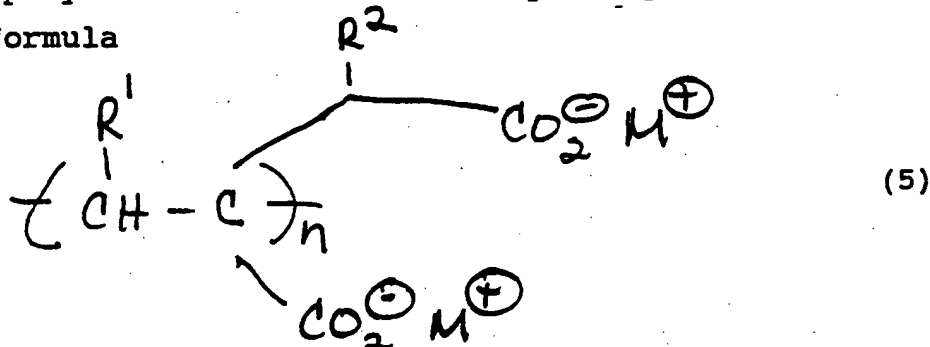
15 30. The method of claim 29 wherein at least some of said positively charged counterions are non-metallic ions comprising, alkyl ammonium, hydroxyalkyl ammonium, choline, taurine, carnitine, guanidine, creatine, adenine, or amino acids or derivatives thereof having a  
20 net positive charge.

31. The method of claim 30 wherein said amino acid comprises glycine, lysine, serine, arginine, alanine, histidine, or aspartic acid.

25 32. The method of claim 29 wherein at least some of said positively charged counterions are metallic ions comprising sodium, potassium, calcium, or magnesium.

- 37 -

33. The method of claim 29 wherein at least one of said polymers is characterized by a repeat unit having the formula



5 or copolymer thereof, where n is an integer,  $M^+$  is an exchangeable counterion other than hydrogen, and each  $R^1$  and  $R^2$ , independently, is H or a lower alkyl group.

34. The method of claim 33 wherein at least some of said positively charged counterions comprise choline,  
10 sodium, hydroxyalkylammonium, or an amino acid or derivative thereof.

35. The method of claim 29 wherein said polymer comprises ethylene-maleic acid copolymer.

36. The method of claim 35 wherein at least some of  
15 said positively charged counterions comprise choline, sodium, hydroxyalkylammonium, or an amino acid or derivative thereof.

37. A therapeutic composition comprising a therapeutically effective amount of one or more  
20 crosslinked polymers that are non-toxic and stable once ingested,

said polymers comprising units having fixed negatively charged polycarboxylate ions, and positively charged counterions other than hydrogen or ammonium which  
25 may be the same or different from each other associated

- 38 -

with said negatively charged ions that are exchangeable with ions in the gastrointestinal tract,

said composition having the property of being non-constipating and non-gritty such that irritation to the  
5 gastrointestinal tract upon ingestion is minimized.

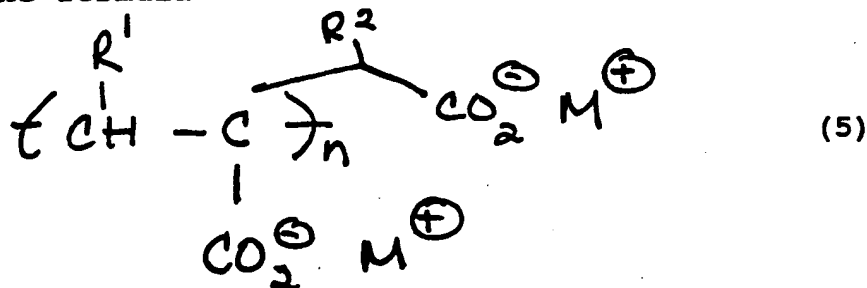
38. The composition of claim 37 wherein at least some of said positively charged counterions are non-metallic ions comprising, alkyl ammonium, hydroxyalkyl ammonium, choline, taurine, carnitine, guanidine,  
10 creatine, adenine, or amino acids or derivatives thereof having a net positive charge.

39. The composition of claim 38 wherein said amino acid comprises glycine, lysine, serine, arginine, alanine, histidine, or aspartic acid.

15

40. The composition of claim 37 wherein at least some of said positively charged counterions are metallic ions comprising sodium, potassium, calcium, or magnesium.

41. The composition of claim 37 wherein at least  
20 one of said polymers is characterized by a repeat unit having the formula



or copolymer thereof, where n is an integer, M<sup>+</sup> is an exchangeable counterion other than hydrogen, and each R<sup>1</sup>  
25 and R<sup>2</sup>, independently, is H or a lower alkyl group.



- 39 -

42. The composition of claim 41 wherein at least some of said positively charged counterions comprise choline, sodium, hydroxyalkylammonium, or an amino acid or derivative thereof.

5        43. The composition of claim 37 wherein said polymer comprises ethylene-maleic acid copolymer.

44. The composition of claim 43 wherein at least some of said positively charged counterions comprise choline, sodium, hydroxyalkylammonium, or an amino acid  
10 or derivative thereof.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US94/04538

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/74

US CL :521/30; 424/78.1

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 521/30; 424/78.1, 78.11, 78.37

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------|---|-----------------------|
| Y         | US, A, 5,114,709 (ST. PIERRE ET AL) 19 May 1992, see entire document.   | 1-44                  |
| Y         | US, A, 4,837,015 (OLSEN) 06 June 1989, see entire document.   | 1-44                  |
| Y         | ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (HEMING ET AL), "CONSIDERATIONS IN THE SELECTION OF CATION EXCHANGE RESINS FOR THERAPEUTIC USE", 1954, see entire document. | 1-44                  |
| Y         | Kidney International Vol. 28, 1985, (MASON ET AL), 'A new ion exchanger with high in vivo sodium capacity', pages 178-182; see entire document.                         | 1-44                  |



Further documents are listed in the continuation of Box C.



See patent family annex.

|   |     |  |
|---|-----|--|
| * Special categories of cited documents:  | *T  | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
| *A* document defining the general state of the art which is not considered to be part of particular relevance   | *X* | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |
| *E* earlier document published on or after the international filing date  | *Y* | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* | document member of the same patent family  |
| *O* document referring to an oral disclosure, use, exhibition or other means  |     |  |
| *P* document published prior to the international filing date but later than the priority date claimed  |     |  |

Date of the actual completion of the international search

10 AUGUST 1994

Date of mailing of the international search report

SEP 06 1994

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

THURMAN K. PAGE

Telephone No. (703) 308-2351